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Intracranial Hodgkin's Disease in Two Patients With Familial Hodgkin's Disease

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Intracranial Hodgkin's disease is very rare and is often a terminal event. The case of a 33-year-old man who relapsed in the anterior pituitary gland without other evidence of disease 6 months after extended field radiation therapy for Stage IIA Hodgkin's disease is presented. He remains well with no evidence of disease five years after surgery and chemotherapy for intracranial relapse. The case of a 16-year-old boy with a dural relapse of Hodgkin's disease associated with positive cerebrospinal fluid cytology is also presented. These two patients are members of different families each with multiple cases of Hodgkin's disease. Central nervous system involvement with Hodgkin's disease may be more frequent in familial Hodgkin's disease in which immune deficiency is common. **Med. Pediatr. Oncol. 28: 255–258.** © 1997 Wiley-Liss, Inc.

Key words: Hodgkin's disease; intracranial Hodgkin's disease; pituitary gland; familial Hodgkin's disease

INTRODUCTION

Intracranial Hodgkin's disease is rare, and relapse with isolated intracranial Hodgkin's disease is extremely rare [1]. We report here the case of a man previously treated with radiation for Stage IIA Hodgkin's disease who was presented 9 months later with relapse with involvement of the anterior pituitary gland as the only site of disease, and that of a 16-year-old boy with dural and cerebrospinal fluid involvement. Both patients were members of families with multiple cases of Hodgkin's disease.

PATIENTS

Case 1

J.L. is a 33-year-old white man who was presented in July 1990 with Stage IIA Hodgkin's disease. A paternal aunt and cousin had previously been treated for Hodgkin's disease. The patient was treated with mantle field radiation with extension to the high para-aortic nodes and boosts to sites of bulky disease. He achieved complete remission and remained well until April 1991 when he was presented with a 10 day history of fever and inability to open his right eye. He had no systemic symptoms. Physical examination revealed fever and right 3rd, 4th, and 6th cranial nerve palsies. MRI of the brain disclosed a mass in the region of the right cavernous sinus with erosion of the clivus (Figure 1). Physical examination and staging of the chest and abdomen failed to identify additional sites of Hodgkin's disease. A lumbar puncture produced normal cerebrospinal fluid. The patient received 300 cGy of radiation to the brain emergently. Further radiation to the region of the sella turcica could not be given since the patient had received the maximum tolerable dose to that region from previous radiation to Waldeyer's ring. He underwent craniotomy and a transsphenoidal biopsy of the enhancing mass noted on MRI in the region of the sell turcica. The histopathology of the lesion was characterized by mononuclear cell infiltration of several tissues including the anterior pituitary gland, dura mater, and adjacent brain parenchyma. Clusters of eosinophils with scattered Leu-M1 and Ki-1 positive Reed-Sternberg cells were readily observed (Figure 2). A diagnosis of Hodgkin's disease was made and the patient was treated with a regimen consisting of oral CCNU 100mg/M^2 on day 1, mitoxantrone 8mg/m^2 days 1–3 and vinblastine 8mg/m^2 days 1 and 21, both given intravenously. His fever and cranial neuropathy resolved completely within two weeks after the first cycle of therapy and he was discharged home. He was re-evaluated after 3 cycles of chemotherapy and no residual disease was detected by neurologic examination or MRI (Figure 3). Chemotherapy was then discontinued due to prolonged grade 4 myelosuppression. The patient continues in complete remission for 62 months as of June, 1996 and has returned to work. His blood counts are normal. He has been on hydrocortisone maintenance following the par-

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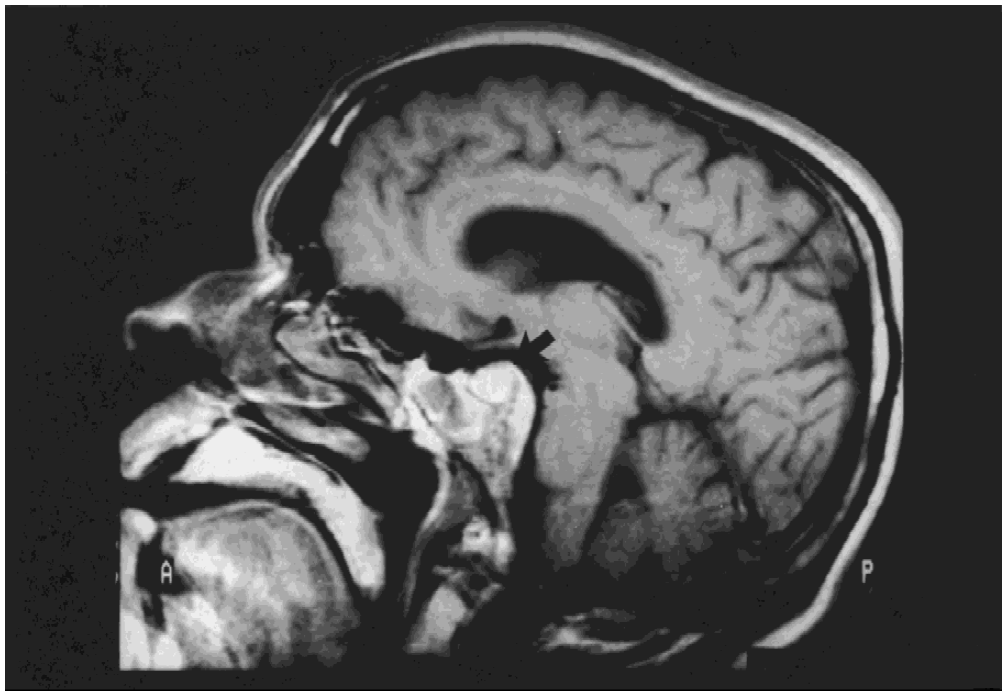

Fig. 1. T1 sagital image showing an enhancing lesion in the region of the sella turcica prior to therapy, see arrow.

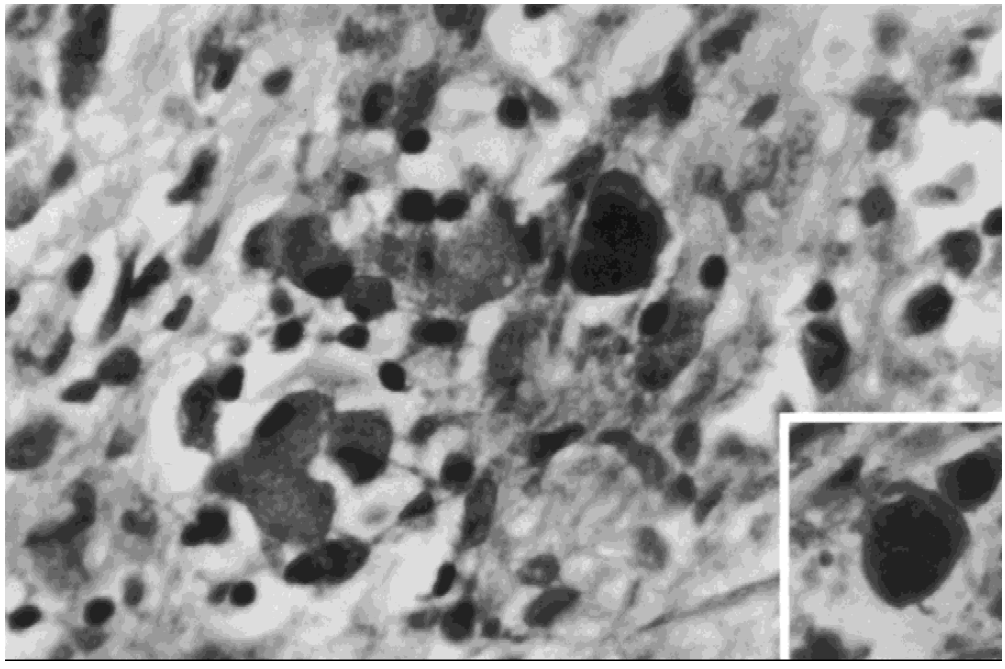

Fig. 2. A few surviving acidophils of the adenohypophysis are seen within the infiltrate of Hodgkin's disease; A well preserved Reed-Sternberg cell is shown in the inset at the right lower corner. H&E stain; 40× magnification.

tial hypophysectomy performed in April 1991. Thyroid and gonadal function tests remain normal.

Case 2

F.P. was a 15-year-old boy in October, 1989 when he was diagnosed with nodular sclerosing Hodgkin's disease, stage IIIB. He was treated with MOPP alternating with ABVD and achieved a complete remission. Six months later mediastinal disease was detected, for which he received radiation therapy to a mantle field. At the completion of that treatment, B symptoms and multiple bone lesions were noted. He then received an allogeneic

Fig. 3. T1 sagital image showing resolution of enhancing lesion previously demonstrated in Figure 1.

bone marrow transplant from an HLA-identical sister, and high-dose chemotherapy. Cyclosporin A and prednisone were given long-term for suppression of graft versus host disease. He again developed B symptoms one year later, as well as bone marrow involvement with Hodgkin's disease. While receiving chemotherapy for that relapse he developed headache and a right temporal superficial mass, which at craniotomy was found to arise from the dura and to invade the temporal lobe. Histologic examination of the mass revealed mixed cellularity Hodgkin's disease. The cerebrospinal fluid was normal. He received cranial irradiation to which the mass completely responded. Three months later the mass recurred and the cerebrospinal fluid examination demonstrated rare but readily identifiable Reed-Sternberg cells as well as numerous mononuclear monocytoid cells. The patient died one month later. On the day that his dural mass was first noted, his 18-year-old sister (not his marrow donor) was diagnosed with stage IIA nodular sclerosing Hodgkin's disease.

DISCUSSION

Intracranial Hodgkin's disease may present as 1) isolated lesion(s) within the brain parenchyma, 2) metastatic to the dura mater with infiltration of subdural neural tissue, 3) metastatic to the dura mater with compression of neural tissue without direct infiltration, or 4) as a lesion of the calvarium with invasion of the dura mater with or without cerebral invasion. Whether at initial presentation or at relapse, the occurrence of Hodgkin's disease intracranially without evidence of disease elsewhere is extremely rare. Williams et al [2] reviewed 1,992 cases of Hodgkin's disease and found neurological complications in 15%, the majority of which were due to extracranial complications. In a review of 7,000 cases of CNS tumor, Zimmerman [3] found only 0.22% were Hodgkin's disease, manifested by either a mass or a diffuse infiltration arising from the meninges. Sapozink and Kaplan [4] reviewed 2,185 cases of Hodgkin's disease and found only 12 cases (0.5%) with intracranial involvement, including two patients with only intracranial involvement. The first published biopsy proven case of isolated intracranial Hodgkin's disease was by Fein and Newill in 1954 [5] and since then, other reports have sporadically appeared [6–11].

It has been postulated that tumor deposits gain intracranial access by contiguous spread through thin lamellar bone at the base of the skull or from involved Waldeyer's ring or upper cervical lymph nodes. However, Sapozink and Kaplan [4] suggested that hematogenous spread was most likely, and Ashby and others [6] proposed spread via emissary veins in a patient with intracranial Hodgkin's disease and a soft-tissue extracranial mass overlying the same site, as in our Case 2. The most common CNS symptoms are cranial nerve palsies, motor and/or sensory deficits, papilledema, headache, coma, and seizures. The cerebral cortex and the meninges, particularly the inferior aspect of the brain, are most frequently involved but no area of the brain appears to be exempt.

Anterior pituitary gland involvement, as in Case 1, has only been reported once previously [6], to the best of our knowledge.

The diagnosis is often suggested by brain imaging techniques such as CT scan or MRI, but biopsy of the lesion is necessary to establish the diagnosis. A lumbar puncture may be helpful if Reed-Sternberg cells or eosinophilia [12] are seen in the cerebrospinal fluid, but they are often absent in the presence of disease. Billingham and others [13] have suggested that lymphoma cells do not exfoliate readily or that the exfoliated cells may not circulate readily in the CSF.

Treatment is usually a combination of cranial radiation, systemic chemotherapy (usually nitrosourea based regimens because of their ability to cross the blood-brain barrier) with steroids, especially, if intracranial pressure is elevated.

Case 1 is unusual in several ways: This patient had anterior pituitary gland involvement without evidence of extracranial disease and he continues in complete remission 61 months after surgery, steroids and 3 cycles of systemic chemotherapy. Although it is impossible to document that chemotherapy was primarily responsible for the successful outcome, it seems unlikely that surgery alone was curative since only a biopsy of the lesion without curative intent was performed. In addition the radiation dose delivered was low in comparison with dosages usually required for eradication of Hodgkin's disease.

Risk factors for intracranial Hodgkin's disease are still unclear. The paternal aunt of Case 1 and her son also had Hodgkin's disease, as did a sister of Case 2. Since familial Hodgkin's disease may be associated with immunodeficiency [14,15], we speculate that intracranial Hodgkin's disease may be related to impaired immunologic status as is primary CNS lymphoma [16]. Intracranial Hodgkin's disease may be more common in familial Hodgkin's disease than previously appreciated. Scheithauer [17] reported the case of a 19-year-old woman with Hodgkin's disease who had a brother and a paternal cousin with Hodgkin's disease as well. That patient developed intraparenchymal Hodgkin's disease of the cerebrum and cerebellum approximately two years after her original diagnosis, in addition to widespread systemic relapse. Furthermore, the case reported by Doorly et al [18] had a cousin with Hodgkin's disease (personal communication, MA Farrell, 1996), and family 11 reported by Razis et al. [19] included a woman with intracranial Hodgkin's disease whose father also had Hodgkin's disease.

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